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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/842,873	04/27/2001	R. Rao Koganty	042881/0156	7911

1444 7590 01/14/2005

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 01/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/842,873	KOGANTY ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *6/17/04*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,16,17,19 and 42-53* is/are pending in the application.

4a) Of the above claim(s) *16,24,25,28,29 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,17,19-23,26,27,30 and 42-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants acknowledged that the response to the restriction requirement filed October 29, 2003 did not traverse the restriction per se. But did traverse the restriction's identification of claim 1 as the only claim generic to all species. In the election, GalNAc from group A, Peptide (either L or D amino acids) from group B, and natural as recited in claim 20 from group C was elected. It was asserted that the claims readable thereon readable on the combined election from A-C) were claims 1-14, 17, 19-22, 26, 27, 30 and Al. The PTO took the position that only claims 1-12, 14, 17, 19-22, 26 and 27 read on the elected species, i.e., it disagreed with Applicant as to the status of claims 13, 30 and 31. Claim 13 has been cancelled, and so for that claim it is a moot point. The Examiner has not explained why claims 30 and 31 lie outside the elected species. The structures associated with malignant cell antigens are clearly "natural" (group C), and at least some of these structures comprise GalNAc (group A). By virtue of base claim 1, as amended June 17, the structures are attached to peptides (group B). Claim 30 as filed is inaptly worded, because it implies that the carbohydrate structures are derived from the bacterial adhesins, when the intent was that they are derived

from the carbohydrate structures of the human glycoantigens which are recognized by those adhesins.

In reply, although claims 30 and 31 are natural ligands however, these are generic claims that can read on other malignant cell antigens not necessarily the elected mucin i.e. comprising some structures besides not necessarily, Gal Nac.

Applicants take the position that claims 23, 24, 25 and 28 are generic to the elected platform (peptides) (see page 9 of June 17, 2004 amendment). The Examiner has failed to explain why this is not the case.

In response, attention is drawn to page 3 of the 7/29/03 Office action. Also, there is no traversal as to why this restriction/election is in error. However, as applicants state the species peptide i.e., linear, cyclic, label and lipidated peptides are all structurally different in that the peptides contain other structures in it e.g., a label or lipid. The linear is structurally different from a cyclic in that the linear peptide can be cyclized in so many structurally different ways e.g., by disulfide or end-to-end cyclization.

Upon request of reconsideration of the species requirement, claim 23 (linear peptide) will be examined with the elected species.

Claims 13, 15-16, 18, 24-25 and 28-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species.

Status of Claims

Claims 1-11, 16-17, 19-31 and 42-53(as presently added) are pending in the application.

Claims 12-15, 18, 32-41 have been cancelled.

Claims 16, 24-25, 28-29 and 31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species.

Claims 1-11, 17, 19-23, 26-27, 30 and 42-53 are under examination.

Withdrawn objections and rejections:

The objection to the drawings with the submission of new drawing figures is withdrawn. The 112, second paragraph in view of the extensive amendments to the claims and 102 rejections over Vetter and 103 over Schleyer et al.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise,

and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Newly amended 1-11, 17, 19-23, 26-27, 30 and added claims 42-53, rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The as-filed specification does not provide support for the now amended e.g., claim 1 and newly added claims 42-53 (6/7/04). For example only, the step of "providing..." is not supported in the as-filed specification. MPEP 714.02 clearly recites that applicants should specifically point out where support in the specification can be found. This is especially true in view of the magnitude of amendments to the claims.

B. Claims 1-11, 17, 19-23, 26-27, 30, (as amended) and newly added 42-53, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mucin 1(MUC1) as the platform and inhibitory activity for a compound in the library, does not reasonably provide enablement

for the broadly recited combinatorially-generated library of glycopeptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons advanced in the last Office action.

Response to Arguments

Applicants state that the Examiner concedes that the specification is enabling for MUCI as the platform, but not for peptides more generally. Applicants argue that the specification clearly contemplates use of platforms other than MUCI. Peptides, and in particular the core proteins of cancer associated mucins, are of particular interest (P1, L9- 13). There is no reason to believe that other peptides would be more difficult to randomly glycosylate than would MUCI. Many different natural glycopeptides are known in the art. Of course, the starting peptide must feature at least one glycosylation site. Platforms are discussed further at P5, L30-P7, L11. The specification says that the platform can be a peptide. Several specific platforms other than MUCI are disclosed. The first is Tn antigen. Since Tn antigen is GalNAc-o-serine, the platform is just Ser per se. TF antigen has the same platform (P7, L30-34). Another platform of interest is the one

shown in Fig. 4. This is a peptide with an unusual bridged structure. Combinatorial chemistry is discussed in a general way.

In reply, the examiner does not controvert applicants' assertion as to the enabling disclosure of MUCI. What is controverted is the other glycopeptides besides the specifically enabled ones. Most of applicants' arguments are as general as the enabling disclosure. It simply repeats what is already generally disclosed in the instant specification. The arguments fail to recite the different natural glycopeptides known in the art i.e., known glycopeptides of undefined structure, as the presently claimed glycopeptides. The specification does not teach how these natural glycopeptides are provided to accomplish the claimed method. If applicants choose to rely upon general knowledge in the art to render their disclosure enabling, applicants must show that anyone skilled in the art would have actually possessed the knowledge, In re Lange (CCPA 1981) 644 F2d 856, 209 USPQ 288, or would reasonably be expected to check the source which applicants rely upon to complete their disclosure and would be able to locate the information with no more than reasonable

intelligence. Applicants can rely upon prior art which would enable one skilled in the art to glean therefrom the necessary information to render the specification enabling with respect to the first paragraph of 35 USC 112 but the burden is on applicant to point out precisely where enablement lies in such disclosure, In re Albrecht II (CCPA 1975) 185 USPQ 590. In this regard, attention is drawn applicants' own work Qui(Tetrahedron Letters, specifically at page 598.) Thus, not everything which may be cited as prior art to preclude the grant of a patent can be equated with common knowledge for the purposes of meeting the enablement requirement of 112. See University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003).

It is further argued that it is clearly taught that for a given platform (peptide), N-glycosylation can occur at the NH2-side chain of Asn, and O-glycosylation at the OH-side chain of Ser, Thr, or hydrolysine. These are "natural glycosylation sites".

In response, there is nothing in the broad claimed steps that recite for said OH or Asn as the glycosylation sites. If NH2 sites are the glycosylation sites, then the N-terminus of

the peptide or other side chain NH2 containing residue can also be included in the broad scope of the claim.

Applicant's further arguments with regard to coverage of unnatural glycosylation sites and etc. are no more than a repetition or list of what is disclosed in the specification.

Applicants further argue that the test of enablement for a method claim is not the number of products which the method can produce, but rather whether the amount of experimentation necessary to practice the method. Combinatorial synthesis techniques, by their very nature, make easy to generate a very large number of different variants. In the peptide library field, libraries with 108-1010 different sequences are routinely synthesized and screened. It would be easy to synthesize more diverse libraries, too. If 20 different amino acids are allowed at each variable position, the diversity of the library is where n is the number of variable positions. Increasing ''n'' is trivial.

In reply, applicants' arguments are confusing, as most of the arguments above are drawn to the products produced by the method. If the object of the method of making is not to obtain a product(millions, as argued) then, the method of synthesizing a product defeats its purpose.

Applicants' arguments as to the glycosylation as shown in Seq. ID. 1 is not controverted. As acknowledged, the synthesis to a particular glycopeptide is enabled and not a glycopeptide of any defined structure or formula as claimed. It is not apparent from the disclosure just how synthesis, i.e., enlarging a carbohydrate structures, as presently claimed, can be accomplished. The broad claimed method is nothing more than an invitation to experiment.

Claim Rejections - 35 USC § 112, second paragraph

Claim 46-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

"The members" of said second level library lacks antecedent basis of support from the base claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the

> differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 5-12, 14, 17, 19-20, 22-23, 26-27 and 42-53 as amended, are rejected under 35 U.S.C. 103 as being obvious over Vetter et al (WO 95/18971) for reasons set forth in the last Office action.

Vetter is discussed in the last Office action.

Response to Arguments

Applicants acknowledge that Vetter et al. (pp. 25-27) discloses the synthesis of glycoconjugate library of the form Ac-X-X-E(OAl)-X-P-resin, where Ac is acetyl, E is Glu, P is Pro, each X is randomly selected from a set of 18 side chain-protected AAs, and "Oal" is the allyl ester protecting group. First, a peptide library (diversity 184) was synthesized. Then it was converted into a glycopeptide library by removing the allyl ester and replacing it randomly with one of a set of 17 glycosylamines (P26, L29-31); these were mono- or disaccharides. Thus, Vetter randomly glycosylated a glycosylation site on A "platform'' (peptide) to create a first level library of glycosylated platforms, per step (a) of claim 1. But argue that claim 1 as amended expressly recites further glycosylation of the first level library to create a second level library.

Scheme IV shows synthesis of the first level of a library, where Tn1, Tn2, Tn3, TFI, TF or TF3 is introduced at either of two glycosylation sites (R, R1). Then Scheme V shows synthesis of a second level library by attachment of G1cNAc to the aforementioned Tn or TF to generate core 61, 62, 21, or 22. The key point here is that it appears that a second level library is intended to be one in which the new sugars are randomly attached to the CHOS of the first library. Such random extension of carbohydrate structure is mandatory in amended claim 1. No such step is disclosed by Vetter.

In reply, attention is directed to page 25, line 33 up to page 27, line 10 wherein Vetter discloses said second level glycosylation. Vetter discloses that after the first set of glycosylating agents e.g., Gal Nac is introduced to the various aliquots of resin beads containing surface reactive functionality to yield a library of glycoconjugates. Aliquots of the original member library were diversified by conjugation to 17 different glycosylamines, inter alia, Gal Nac. See further page 6, lines 1-25 i.e., where the repetitive steps of adding glycosyl residues (as in the peptide) is disclosed. Applicants' further arguments as to scheme IV and V is not commensurate in scope with the claims. The claims do not recite for said Tn structure or any structure of any of the components.

Claims 1-2, 5-14, 17, 19-23 and 26-27 are rejected under 35 USC 103 as being obvious over Schleyer et al for reasons advanced in the last Office action.

Response to Arguments

Applicants acknowledged that Schleyer carried out glycosylation of the peptides with one of three sugars. But argue it does not appear that the sugar was randomly selected. Thus, we do not agree with the Examiner that Schleyer teaches random variation of the sugar. Even if we did, there is no teaching of second level variation which, as we have explained, is different from just glycosylating an unglycosylated peptide with two different glycosylation sites.

In response, attention is drawn to page 1976 col. 1 which recites that "currently the most efficient method to synthesize glycopeptides is by solid phase synthesis with glycosylated amino acid building blocks…"(i.e., providing a first level, as claimed)……it has been demonstrated that solid phase bound glycopeptides and oligosaccharides with free hydroxyl groups on the oligosaccharide moiety could be glycosylated with <u>different glycosyl</u>…" (Underlinings supplied). Thus, the suggested teaching of Schleyer et al that free hydroxy groups on the oligosaccharide moiety could be glycosylated with different

glycosyl would obviously result in the lengthening of the carbohydrate structures, as claimed.

Claims 1-2, 5-14, 17, 19-22, 26-27 and 42-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rao (U.S. 5,795,958) for reasons advanced in the last Office action.

Response to Arguments

Applicants admit that Rao creates a glycopeptide library using fucose-serine building blocks. No amino acid other than serine is glycosylated, and no sugar other than fucose is disclosed. Thus, there is no randomness in Rao's glycosylation step. Rather, the randomness is in the amino acids to which the Fuc-ser is attached. The Examiner seeks to overcome this problem by reference to prior art cited by Rao, notably Peters et al. (1992). The citation refers to use of protected Ser and Thr building blocks, but does not say what sugars were attached, and whether the sugars were randomized. Peters, et al, as argued, describes stepwise solid-phase synthesis of glycopeptides using already glycosylated amino acids as building blocks. Only one carbohydrate structure (GalNAc) was employed. A multiple column peptide synthesizer was used for simultaneous assembly of forty different glycopeptides. These glycopeptide varied in amino acid sequence (see Fig. 1), and hence in the

location of the carbohydrate structures, but the only carbohydrate structure employed was GalNAc. There was no randomization of the carbohydrate structures.

In reply, Rao discloses even only at least GalNAc randomization at different residues thus creating random glycopeptides. The claims do not recite for any sugar at least claim 1. Furthermore, there is no claim step that recites that the random glycosylation results in the enlargement of carbohydrate residue except for the thereby clause of enlarging the carbohydrate structures.

Claims 3-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vetter or Rao or Schleyer in view of Ding et al (Cancer Immunology Immunotherapy) for reasons set forth in the last Office action.

Response to Arguments

Applicants acknowledge that Ding discloses the utility of the MUCI sequence recited in claim 3. But argue that the primary references do not render obvious the second round glycosylation step of claim 1, and this deficiency is not addressed by Ding.

In response, Ding at page 10, col. 1 discloses or at least suggest that MUC1-encoded mucins expressed on various cancers contain the same tandem repeat core peptide sequence, glycosylating difference do exits. See further Fig. 1. Ding at

page 15 under the Discussion heading discloses that Epiglycanin has repeating TF and Tn carbohydrate epitopes. Accordingly, it would have been obvious to one having ordinary skill in the art to glycosylate the O-glycopeptide with one or more glycosyl acceptor since Ding discloses or at least suggests that TF and Tn has repeating carbohydrate epitopes. Furthermore, as Schleyer suggested carbohydrate with free OH can be further glycosylated.

As apparent from the teachings of Rao, iterative synthesis by addition of one or more residues results in the lengthening of the desired residues. The various cited art has disclosed that synthesis can be done either in the core peptide or carbohydrate residues that results in a library production of the glycopeptides. Chemical synthesis of peptides or carbohydrates or glycopeptides, either singly or in library form, by addition of a single or fragment residues to a given structure, have advanced markedly that to date it has now been automated. There is nothing novel in the chemical synthesis of a mimic of a natural glycopeptides when the natural proteins are known to already contain repeating carbohydrate epitopes, as taught by Ding.

It is argued, with respect to claim 4, Ding does not single out the GSTA as significant. So this claim offers a further distinction.

In reply, with the use of the term "comprising" in the claim, other residues present in the GSTA of Ding is not precluded. Furthermore, it is not clear how randomization of a plurality of carbohydrate can occur in a single OH group, Ser in the GSTA peptide.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims 13, 15-16, 18, 24-25 and 28-31 drawn to a nonelected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is(571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw
January 12, 2005